REMARKS

Applicant's attorney wishes to thank Examiner Qazi for the courtesies extended during the interview of December 17, 2002.

Claims 1-15 currently appear in this application. The Office Action of September 10, 2002, has been carefully studied. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicants respectfully request favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

Priority

The specification has been amended to refer to the earlier filed application.

Information Disclosure Statement

Contrary to the Examiner's assertion, an Information Disclosure Statement was filed in the instant case on April 16, 2002 and October 23, 2002. Submitted herewith are copies of the Information Disclosure Statements, along with a copy of the receipt cards bearing the PTO stamp as evidence of these IDSs having been filed. This is a true copy of the IDS filed April 16, 2002 and October 23, 2002.

Art Rejections

Claims 1-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Miyamoto et al.

Claims 1-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Posner et al.

Claims 1-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Ono et al.

This rejection is respectfully traversed. As discussed during the December 17 interview, neither Miyamoto et al. or Ono et al. disclosed any 2α derivatives of vitamin D; all of the derivatives disclosed therein were β derivatives.

The claims have been amended to overcome the rejection over Posner et al.; all of the claims now limit R^2 to C_{1-4} alkyl or C_{1-3} hydroxyalkyl.

Claims 1-15 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Miyamoto et al.

This rejection is respectfully traversed. As noted above, Miyamoto et al. only show β derivatives of vitamin D, whereas the compounds of the present invention are all alpha derivatives. The 2-α derivatives of the instant invention have much higher vitamin D receptor (VDR) binding properties than the 2-β derivatives of Miyamoto.

For example, test example 1 of the instant application shows that the binding property of the 2a-hydroxypropyl vitamin D derivative (compound 33) is 300, and that of the 2α-ethyl vitamin D derivative (compound 34) is 40. According to Ono, page 1628, Figure 1, and Tsugawa et al., page 70, Table 2, code names HAK-3 and AK-2, reported in *Biol. Pharm. Bull* **23(1)**, 66-71, 2000, the binding property of the corresponding 2-β-hydroxypropyl compound and the 2-β-ethyl compound is 138 and 10, respectively, which values are much lower than those of the 2α vitamin D derivatives of the present invention.

Suhara et al., page 8763, compound 9 of Table 1, *J. Org. Chem.* **66**, 8760-8771, 2001, reported the binding property of the 2α-butyl compound of the instant invention as 8. According to Tsugawa, page 70, Table 2, code name AK-4, the binding property of the corresponding 2β-butyl compound is 0.9, which is much lower than the 2α derivative of the present invention.

The 2α derivatives have been demonstrate to show superior VDR activity to the 2b derivatives of Miyamoto et al.

As noted at the December 17 interview, the inventors of the instant application (Suhara, Takayama, Fujisima, and Konno) are the co-authors of the Suhara et

al. articles discussed above. In this document, the VDR binding property was determined by the same method as in Test Example 1 of the instant application. This test is described in Suhara on page 8763, right column, lines 8-11 from the bottom, that is, it is the method described in Imae et al. (section 2.3, right column, page 303 *Biochim. Biophys. Acta*, 1213, 1994). This method is substantially the same method as used in the instant application.

There is a question as to whether Posner et al. actually synthesized or did not completely purify the 2α-hydroxypropyl vitamin D derivative disclosed therein, since the VDR binding activity of the 2-α-hydroxypropyl vitamin D derivative (compound 33 of the present invention) reported by Posner is extremely low as compared with the VDR reported by Suhara et al., *supra*.

Since Posner discloses that the 2α-hydroxypropyl vitamin D derivative has extremely low VDR binding activity as compared with active Vitamin D3 (1α, 25-dioxyvitamin D3), page 20, it is respectfully submitted that one skilled in the art would not be motivated to synthesize other 2α-hydroxyalkyl vitamin D derivatives when they are seeking to prepare compounds with higher VDR binding activity.

The corrections of inadvertent typographical errors in the specification does not add new matter, but is merely the result of an incorrect translation. The Japanese priority document supports these corrections.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

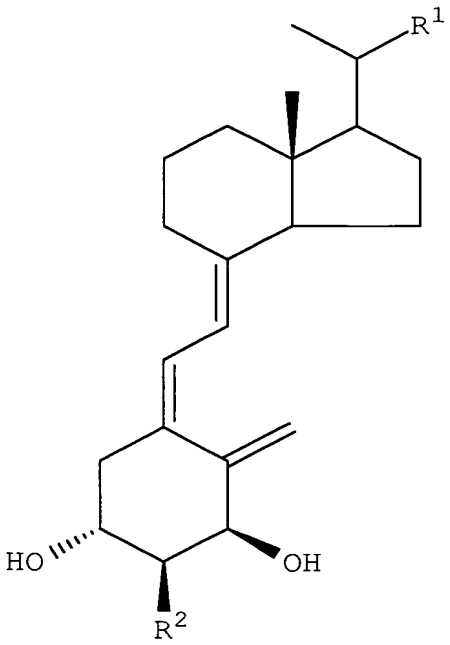
BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By _____
Anne M. Kornbau
Registration No. 25,884

AMK:nmp
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\Y\YUAS\Takayama10\PTO\jan 10 03 amend.doc

"Version with markings to show changes"

1. (Amended) A vitamin D derivative represented by Formula (I):



(I)

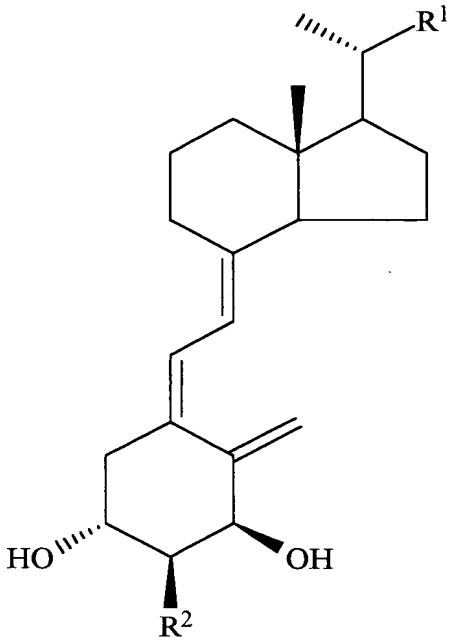
wherein

R^1 represents a saturated aliphatic $C_{1\sim15}$hydrocarbon group optionally substituted with 1 to 3 hydroxy or protected hydroxy groups; and

R^2 represents a saturated aliphatic ~~$C_{1\sim10}$hydrocarbon~~ **C_{2-4} alkyl or C_{1-3} hydroxyalkyl** group optionally substituted with one or more substituents, which may be the same or different and which are selected from the group consisting of a hydroxy group, a halogen atom, a cyano group, a lower alkoxy group, an amino group and an acylamino group, provided that when R^2 represents a

saturated aliphatic C_1hydrocarbon group, R^2 is substituted with at least one substituent.

2. (Amended) The vitamin D derivative of claim 1 which is represented by Formula (II):



(II)

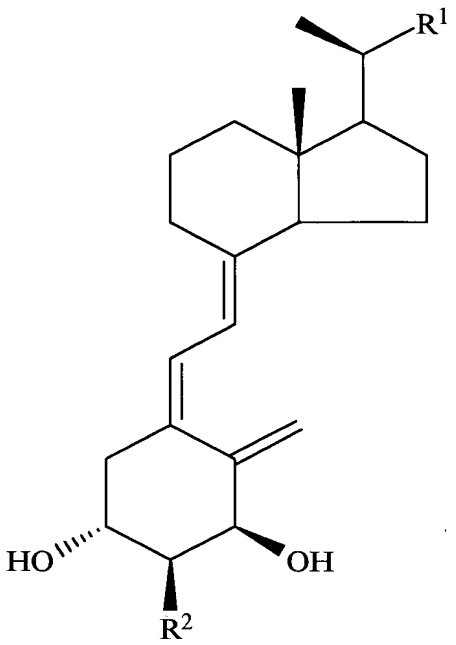
wherein

R^1 represents a saturated aliphatic $C_{1\sim15}$hydrocarbon group optionally substituted with 1 to 3 hydroxy or protected hydroxy groups; and

R^2 represents a ~~saturated aliphatic $C_{1\sim10}$hydrocarbon~~ **C_{2-4} alkyl or C_{1-3} hydroxyalkyl** group optionally substituted with one or more substituents, which may be the same or different and which are selected from the group consisting of a hydroxy group, a halogen atom, a cyano group, a lower alkoxy group, an amino group and an

acylamino group, provided that when R^2 represents a saturated aliphatic C_1hydrocarbon group, R^2 is substituted with at least one substituent.

3. (Amended) The vitamin D derivative of claim 1 which is represented by Formula (III):



(III)

wherein

R^1 represents a saturated aliphatic $C_{1\sim15}$hydrocarbon group optionally substituted with 1 to 3 hydroxy or protected hydroxy groups; and

R^2 represents a saturated aliphatic ~~$C_{1\sim10}$hydrocarbon~~C_{2-4} **alkyl is a C_{1-3} hydroxyalkyl** group optionally substituted with one or more substituents, which may be the same or different and which are selected from the group consisting of a hydroxy group, a halogen atom, a cyano

group, a lower alkoxy group, an amino group and an acylamino group, provided that when R^2 represents a saturated aliphatic C_1hydrocarbon group, R^2 is substituted with at least one substituent.

4. (Amended) The vitamin D derivative according to one of claims 1 to 3, wherein R^2 is a hydroxymethyl group, a hydroxyethyl group, a hydroxypropyl group, ~~a hydroxybutyl group, a hydroxypentyl group, a hydroxyhexyl group,~~ an ethyl group, a propyl group, a <u>or</u> butyl group~~, a pentyl group or a hexyl group~~.

6. (Amended) The vitamin D derivative according to claim 1 selected from the group consisting of

(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-hydroxymethyl-1,3,25-triol,

(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(2'-hydroxyethyl)-1,3,25-triol,

(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(3'-hydroxypropyl)-1,3,25-triol,

~~(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(4'-hydroxybutyl)-1,3,25-triol,~~

~~(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(5'-hydroxypentyl)-1,3,25-triol,~~
~~(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(6'-hydroxyhexyl)-1,3,25-triol,~~
(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-ethyl-1,3,25-triol,
(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-propyl-1,3,25-triol, **and**
(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-butyl-1,3,25-triol,
~~(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-pentyl-1,3,25-triol and~~
~~(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-hexyl-1,3,25-triol~~.

8. (Amended) The pharmaceutical composition according to claim 7, wherein the composition ~~is a therapeutic agent~~**includes an effective amount of a vitamin D derivative according to any one of claims 1 to 6 as an active ingredient** for a disease associated with abnormal calcium metabolism, an antitumor agent or an immunomodulator.

13. (Amended) The pharmaceutical composition according to claim 10, ~~wherein the composition~~

~~is~~**comprising an effective amount of** a therapeutic agent for a disease associated with abnormal calcium metabolism, an antitumor agent or an immunomodulator.

14. (Amended) The pharmaceutical composition according to claim 11, ~~**wherein the composition**~~ ~~**is**~~**comprising an effective amount of** a therapeutic agent for a disease associated with abnormal calcium metabolism, an antitumor agent or an immunomodulator.

15. (Amended) The pharmaceutical composition according to claim 12, ~~**wherein the composition**~~ ~~**is**~~**comprising an effective amount of** a therapeutic agent for a disease associated with abnormal calcium metabolism, an antitumor agent or an immunomodulator.